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A review of the concepts, recent advances and niche applications of the (photo) Fenton process, beyond water/wastewater treatment: Surface functionalization, biomass treatment, combatting cancer and other medical uses

Stefanos Giannakis*

School of Basic Sciences (SB), Institute of Chemical Science and Engineering (ISIC), Group of Advanced Oxidation Processes (GPAO), École Polytechnique Fédérale de Lausanne (EPFL), Station 6, CH-1015 Lausanne, Switzerland

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Dedicated to the occasion of Prof. Cesar Pulgarin's retirement from École Polytechnique Fédérale de Lausanne (EPFL), Lausanne, Switzerland.

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ABSTRACT

The Fenton reaction was discovered over 120 years ago, yet our understanding of the complete reaction mechanism of the seemingly simple iron and hydrogen peroxide reaction ($Fe + H_2O_2$) remains unclear, thus limiting its full potential. In this work, the aim is to summarize the processes that pertain to the (photo) Fenton reaction. More specifically, this review does not consider previous work relating to the Advanced Oxidation Process (AOP)-mediated disinfection/decontamination of stream flows, as much work has successfully achieved this. Instead, this manuscript presents an overview of the other fields of environmental and medical applications of (photo)Fenton: i) surface pre-treatment (nano-particles functionalization or modification), ii) terrestrial and algal biomass (pre)treatment to enhance high value products' recovery, iii) cancer treatment (malignant tumor elimination) and iv) other medical uses (antibiotics development, wounds disinfection, root canal sterilization and teeth whitening). For each field of application, the focus lies on analyzing the conceptualization and framework of the (photo) Fenton process, the opportunities and limitations, as well as a series of related applications. To conclude, the work discusses the current limitations of the existing applications and future research avenues.

1. Introduction: the (photo)Fenton process, and the opportunities beyond water and wastewater treatment

In 1894, H.J.H. Fenton made an unforeseen discovery that revolutionized the research agenda for future generations of scientists. Iron, in combination with oxidizers was found to oxidize tartaric acid, leading to the exploration of the chemical nature of this process. The set of reactions, named after Fenton himself (Fenton process [1]), could be broadly described by two main reactions: the oxidation of iron with the simultaneous production of hydroxyl radicals ($HO^{\cdot}$), and the iron reduction back to Fe^{2+}, which is the limiting step of the process (Eqs. 1, 2):

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + HO^{\bullet} + OH^{-} \tag{1}$$

$$Fe^{3+} + H_2O_2 \rightarrow Fe^{2+} + HO_2^{\bullet} + H^{+} \tag{2}$$

Nevertheless, this scheme does not fully describe the process, in which a series of radical propagation reactions, as well as self-inhibition, take place. The reality is far more complex, but for the purpose of this review there will be no further analysis of the chain reaction (interested readers should refer to [2]). What should be made clear is that the Fenton process has typically been considered to be a highly effective reaction at acidic pH, since the iron aqua-complexes are insoluble at higher pH values and rather weak above pH 4. However, the presence of organic ligands facilitates the complexation of iron and the realization at slightly higher values, as well as the beneficial presence of light, which via a ligand-to-metal charge transfer process (LMCT) aids in the regeneration of Fe^{3+} to Fe^{2+}, converting it into a photo-catalytic process (Eqs. 3,4):

$$[Fe^{3+}(OH)(H_2O)_5]^{2+} + H_2O \xrightarrow{hv\ (LMCT)} [Fe^{2+}(H_2O)_6]^{2+} + HO^{\bullet} \tag{3}$$

$$[Fe(COO-R)]^{2+} \xrightarrow{hv\ (LMCT)} Fe^{2+} + CO_2 + R^{\bullet} \tag{4}$$

Since the (photo)Fenton process applications were thought to be conceptually limited by the pH in the water, the majority of

* Corresponding author.
E-mail address: Stefanos.Giannakis@epfl.ch.

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applications dealt with chemical contaminants' degradation in wastewater flows. The field has seen milestone papers, such as the reviews of Neyens and Bayens [3], Pignatello and co-workers [4], which contributed to a deeper understanding of the field. Only a decade later, reviews focused on water treatment or the homogeneous process at higher pH [5,6].

Besides the chemical decontamination of (waste)water flows, disinfection is historically a more recent field that emerged within the domain of the Fenton applications. After the seminal work of Rincon and Pulgarin [7], which demonstrated the effectiveness of the Fenton process at near-neutral pH, a new field was opened and has been enriched by works on the disinfection of: i) simpler microorganisms (recently reviewed [5,8]), such as bacteria [9–13], viruses [14–16], protozoa [17], ii) higher order ones, like algae [18], yeasts and fungi [19,20], iii) complex microbial communities like biofilms [21] and iv) special bacterial cases, such as antibiotic resistant microorganisms [22]. Nevertheless, although the discovery of the Fenton reaction originates in Chemistry, its most well-known works (reviews) originate from the field of Biology [23,24].

Looking forward, the Fenton process was and still is an intriguing field of study. Regardless of the type of application, the fundamentals of the process remain the same. The versatile, modular character of the Fenton process makes it open and amenable to an array of different fields, ranging from medicine to reactor design. The present review will focus on the most recent advances and applications of the Fenton process, namely i) its use as an efficient method for surface pre-treatment and functionalization (nano-particles, nano-tubes, quantum dots as well as industrial synthetic and bio-compatible materials), ii) as an alternative means of terrestrial and algal biomass pre-treatment for the enhancement of recovery of high-value products, iii) the first promising alternative method of cancer treatment and iv) the utility in other biomedical uses (trauma disinfection, antibiotics, dental care and aesthetic dentistry). In order to provide a complete overview of the issue, the conceptual framework for each topic will be presented first, followed by a discussion of its link with the fundamentals of the Fenton process. Finally, the relevant applications in each subject will be presented.

2. Surface pre-treatment, modifications and functionalization of materials

2.1. Functionalization and preparation of carbonaceous materials: diamond nano-particles (DNPs), multi-walled carbon nano-tubes (MWCNTs) and graphene quantum dots (GQDs)

Diamond Nano-Particles (DNPs), Multi-Walled Carbon Nano-Tubes (MWCNTs) and Graphene Quantum Dots (GQDs) represent some of the most promising advances in material science, with the potential applications ranging from structural to (bio)medical and environmental ones. These materials can greatly benefit from the application of a (photo)Fenton pre-treatment. In principle, DNPs are produced on a large scale by the denotation of explosives, a simple and cost-effective process [25–27]. Nevertheless, their direct use is inhibited by carbonaceous material, namely "soot matter", which hinders DNPs solubility and functionalization [26]. Recent studies have demonstrated that pre-treatment of DNPs with the Fenton process not only removes soot matter, but also allows the anchoring of side-chains (e.g. aromatic rings or alkyls [28]), deposition of metals [29] as well as the functionalization with dyes and paired with plasmids [27]. The differences between the non- and pre-treatment matter are compelling and enhanced high transmissibility towards the cell nucleus were observed, which maintained a good bio-compatibility [27]. MWCNTs, on the other hand, represent a group of inert and insoluble materials. Hence, increasing their dispersion capacity in aqueous media is of great importance. By applying the photo-Fenton process, the MWCNTs were oxidized and functionalized by the addition of oxygen-containing groups, such as carboxyl and hydroxyl groups [30,31]. With respect to GQDs, their discovery has paved the way for a series of in vivo and in vitro applications due to their unique physicochemical characteristics [32–34]. Hence, a method for easy and massive production, as a replacement to the existing time consuming, inefficient and damaging graphene oxide (GO) treatment methods, were called for [34]. As such, since (GO) has practically the same properties of an aromatic molecule, it can react with the photo-Fenton process and when the process is prolonged, small molecules are generated from the decomposition of the large GO sheets to smaller parts and finally the GQDs [35].

The mechanism of the transformation can be described as follows: The concomitant presence of Fe and H_2O_2 generates $HO^{\cdot}$ radicals, which is greatly enhanced in the presence of UV light. $HO^{\bullet}$ adds to the defects on the surface of the materials, as well as the C=C bonds [30]. The possible mechanism involves the direct oxidation and mineralization of carboxylic acids (if present), or the electrophilic addition of hydroxyl groups into unsaturated bonds, their conversion to quinones and the subsequent transformation to carboxylic acids, which are prone to mineralization [36]. The proof of the attacks come from the disappearance of soot matter and decrease in particle size, with increasing solubility [27], as measured by IR [27] or tandem MS and NMR spectra [35] that corroborate the generation of HO- and carboxyl-rich structures for DNPs and MWCNTs respectively. The reaction stops when significantly low hydroxyl and/or epoxy groups are encountered in GQDs, which are comprised of carboxylic groups on aromatic rings [35]. A brief overview of the processes is given in Fig. 1.

2.2. Pre-treatment of raw matter for manufacturing of industrial and bio-compatible materials

The (photo)Fenton process finds application in the preparation of industrial synthetic or special biomedical materials (implants). For example, in the fabrication of medium-density fiberboard (MDF), it can play a key role in the adhesion of the material. Firstly, the MDF process was adapted in order to salvage the waste of wood species, and utilize lignocellulosic fiber [37]. During the processing stages, specifically the hot-pressing of the wheat straw, resins based on formaldehyde are normally used, which raises environmental concerns. Hence, oxidizing the fiber surface could create the necessary covalent bonds in the polymer, due to high intra- and inter-fiber interactions [37,38]. The activation takes place via the $HO^{\cdot}$-mediated oxidation of lignin and other carbohydrates in the fiber, as well as inside the cell walls due to the reactivity of lignocellulosic radical species [37]. In a similar manner, the production of micro-fibrillated cellulose (MFC) by pressure homogenization involves a series of downsides, such as the energy consumption [39]. Solutions such as enzymatic hydrolysis, high pressure, TEMPO oxidation and carboxy-methylation have been examined [40,41], but the chemical demands clash with the environmental concerns. The Fenton process followed by mechanical treatment yielded MFC with a high number of carbonyl groups and viscosity, as well as stable water performance [39]. The pretreatment with the Fenton process in acidic conditions can decrease the energy demand of mechanical treatment due to the enhanced specific surface area, and has comparable characteristics/properties to the enzymatically pre-treated bleached birch kraft pulp [39]. Finally, the Fenton process can enhance the key properties of bio-materials, such as shape memory alloys (SMA), destined for human implant use, such as the NiTi SMA [42]. In particular, the problems that need to be addressed include the mechanical stability, the release of Ni, the deposition of blood platelets, the corrosion inhibition, and its biocompatibility [42]. For this purpose, oxidation has been applied to cover the alloy with Ti in order to prevent the leaching of Ni [42,43] and to increase the wettability of the surface to prevent thrombosis [44]. It has been shown that the pre-treatment of a NiTi SMA with the Fenton process (and subsequent boiling) has improved its properties, including mechanical stability and good coverage with Ti, which implies the reduction of electrochemical corrosion and adsorption of clots expected in physiological conditions. The final

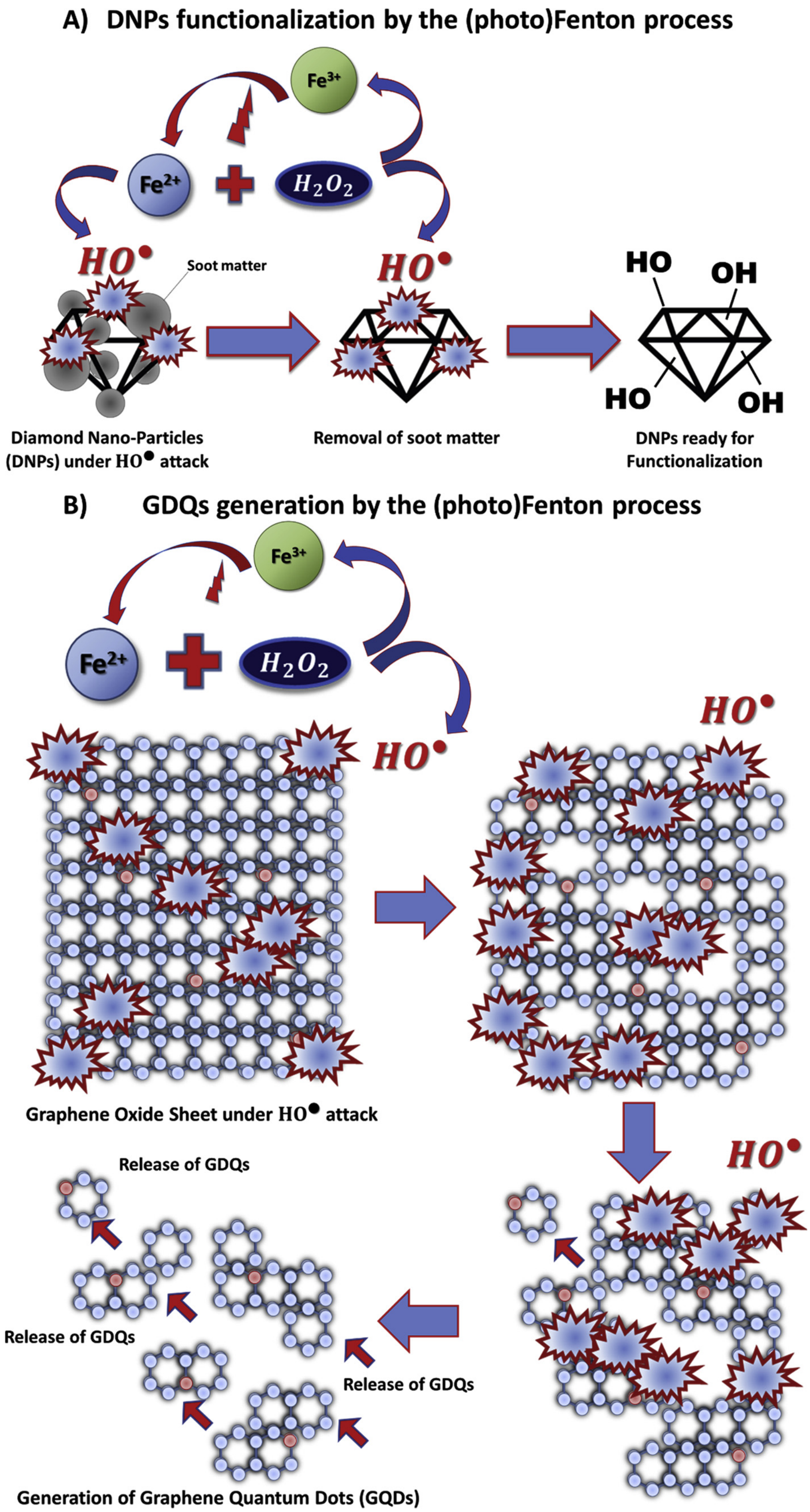

Fig. 1. Application of the (photo)Fenton process for surface treatment. A) Application of the (photo) Fenton process for Diamond Nano-Particles treatment (soot matter removal and functionalization). The hydroxyl radical-mediated attacks remove soot matter from the DNPs while hydroxylation makes them ready for subsequent functionalization (Adapted from [27]). B) Generation of Graphene Quantum Dots. Starting from a Graphene Oxide sheet, exposure to oxidative stress by the (photo) Fenton process slowly detaches small molecules from its body (GDQs) (Adapted from [34,35]). Light in both cases could be used to photo-reduce iron and restart the photo-Fenton cycle.

material was considered to perform as well as plasma pre-treated and superior to oxidation in high temperatures [42].

3. Terrestrial and algal biomass treatment: the (photo) Fenton process as a means of added value products recovery

3.1. Terrestrial biomass processing

Faced with increasing energy demands, the scientific community was faced with the need to find a viable alternative to fossil fuels that was sustainable and responded to the ever-increasing environmental concerns [45]. A green alternative was found at biomass in its utilization as a material for fuel production. Biomass is defined as a "non-fossil, energy containing form of carbon" [46] and within this intrinsically energy-containing material, all terrestrial- or water-based vegetation and bio-solids (sludge) can be included. As such, biomass has been assessed as a potential raw matter for liquid or gas fuel with the purpose of generating either electricity or heat [47–49]. This material is comprised of polysaccharides from cell walls (cellulose, hemicellulose) that are the main desired products destined for fuel production, lignin [50] and other proteins/nucleic acids (but in lesser extent) [51,52].

Nevertheless, it was quickly found that raw biomass was an incompatible substrate for energy or high-value products generation, since lignin seals the cell with a recalcitrant structure [52–55]. This is a necessary natural precaution to prevent natural enzymatic degradation of the carbohydrates [56,57]; hence pretreatment should be applied. The processes that have been predominately applied to biomass pretreatment involved biologic and physicochemical ones (reviewed in [51]), some of which involve high temperatures (~200°C), acids, catalytic oxidation or reduction and/or enzymatic hydrolysis. These methods have often been linked with undesirable byproducts which are costly or can block the downstream enzymatic fermentation process of the sugars [58–60]. Consequently, the need to develop a mild, green but effective method was necessary; this process had to be mild towards cellulose, reduce the size of biomass and produce no inhibitory compounds [52,61,62].

Over the past few years, the (photo)Fenton process has found a potentially influential application in the pre-treatment of biomass. This idea stems from the natural phenomenon taking place in plants, with lignin-containing cell walls by fungi [61,63,64]. In this process, which can be observed in brown-rot fungi, a $HO^{\cdot}$-mediated attack takes place, thanks to a non-enzymatic Fenton process, and materializes in the cleavage of lignin (hydroxylation and methoxylation [45,65]) and the oxidation glycosylic bonds of the holocellulose [61]. The Fenton reagents (both Fe and H_2O_2) can penetrate the non-crystalline structures of the cell wall and thus facilitate a reduction in the lignin strength before its destruction [66–68]; this process is highly selective and causes low lignin removal, while liberating the cellulose contents. A schematic representation of the process is given in Fig. 2. Ultimately, access to cellulose beyond the lignin barrier allows higher recovery and subsequent enhanced yield of enzymatic hydrolysis [49,60].

Considering the aforementioned advantages, the Fenton pretreatment process has found a number of significant applications in biomass valorization. Applying the Fenton reaction after the hydrolysis of biomass eliminated toxic compounds increased 95% the ethanol yield [60]. In a test with various biomass origins, pre-treatment with the Fenton process (in acidic conditions) achieved high delignification (up to 62.3%) with the subsequent concentration of volatile fatty acids being high enough to produce biogas; when the Fenton process was combined with enzymatic treatment, the glucose contents were > 4 g/L [49]. In a similar manner, i.e. in homogeneous Fenton treatment, saccharification increased by more than 200% and induced x3 gas production [52]. Nevertheless, these works involved relatively low load, and the problem was soon addressed; at 25°C and 10% load, the enzymatic digestibility that followed the Fenton pre-treatment reached close-to-ideal yield [64]. Other combinations of the Fenton process involved i) the downstream alkaline extraction, which caused, among other effects, porosity and crystallinity changes in the biomass body, without the generation of undesired by-products for fermentation [55], ii) the hydrothermal treatment after the Fenton process, which showed negligible loss of treated biomass (in weight terms) and a 10% higher conversion of cellulose compared to the untreated sample [68], or in an inverse manner iii) dilute acid application (for cellulose hydrolysis) and Fenton process for lignin depolymerization; a high sugar yield was achieved with low amounts of enzymes. Finally, some additional advantages of and avenues for the Fenton process application include the lack of Fe recovery, as it was not found to be a hindering factor [49]. Also, in the cases of sequential treatment, if acidic pre-treatment is applied, the need for acidification to apply the homogeneous Fenton reaction becomes lower, and in the case of dilute NaOH post-treatment, this can recover the low pH values necessary for efficient Fenton application.

As a parallel research axis in pre-treatment by the Fenton process, several modifications of the homogeneous biomass treatment have been carried out. For example, the valorization of wastes was attempted, by using garden biomass, which consisted of floristry products or the aesthetic treatment/maintenance of green zones [69]; the amounts of cellulose and hemicellulose are enough to sustain the downstream processes, while treatment-wise no significant changes in reactants' concentration are proposed. Furthermore, the ultrasonic processes have often been considered as a complementary or synergistic process to the Fenton reaction [70–72]. In biomass pre-treatment, it has been shown to improve 9% of the subsequent cellulose saccharification, due to the sono-catalytic cycle of Fe, maintained by cavitation, in both lignin and cellulose modification [73]. Furthermore, in the era of nano-materials, the Fenton-mediated treatment of biomass was not an exception. The exceptional properties of nano-oxides [74,75], and specifically magnetite (Fe_3O_4), enhanced the glucose production in various starting biomass materials [75]; their magnetic character suggests a reusability and easy separation from the bulk, thus potentially decreasing the process' costs. Alternatively, in order to avoid the acidification steps while maintaining good catalytic activity, ligand-mediated Fenton has been utilized [76]. The use of ligands in Fenton process increases the solubility of Fe species, creates photo-active complexes and allows their use in circumneutral pH. It was found that chelation with citric acid decreased the holocellulose destruction during pre-treatment, enhanced the regeneration of Fe^{3+} back to Fe^{2+}, but brought about an increase in the activity of the saccharification enzymes involved, thus increasing sugar yields [76]. Finally, although most previous research involves pre-treatment in order to increase the accessibility of the holocellulose, the valorization of lignin has also been assessed. In this process, lignin was depolymerized by a Fenton system in supercritical ethanol, producing oils [45], while a "selective lignin depolymerization" Fenton/supercritical ethanol process has been developed to first depolymerize lignin, preserving the holocellulose, and achieving high phenolic oil production and sugars [77]. In conclusion, it is clear that pre-treating terrestrial biomass by the Fenton process entails a cost effective and environmentally friendly way to facilitate the recovery of high-value products.

3.2. Algal biomass processing

In addition to terrestrial biomass, algal biomass has been scrutinized under the guise of producing high- or added-value products, such as lipids (for fuel production). The idea behind the (photo)Fenton application for algal biomass pre-treatment does not significantly differ in concept to the one of terrestrial origin; an extracellular oxidative stress is applied to the algae, attacking the components of the cell wall, such as saccharides, cellulose etc. [78], and facilitating the release of the triaglycerols, the biodiesel precursors [79,80] into the bulk. What differs from the terrestrial biomass is the added value product recovery,

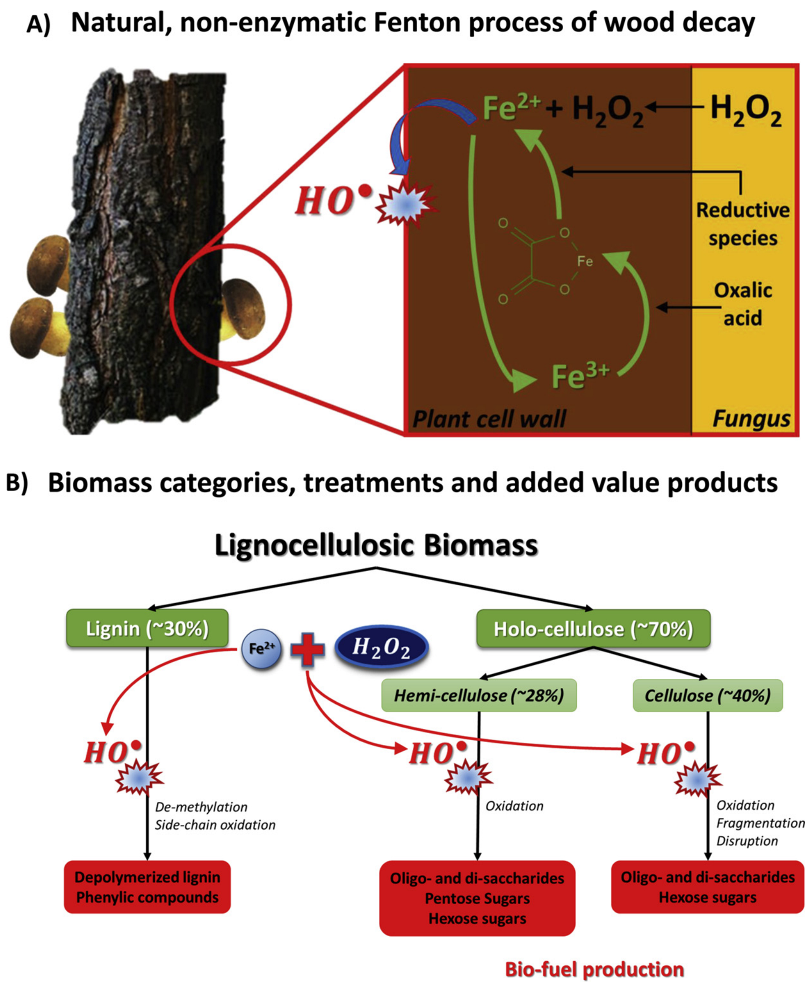

Fig. 2. Application of the (photo)Fenton process for biomass (pre)treatment. A) The natural Fenton process initiated by brown rot fungi involves the release of H_2O_2, oxalic acid and reductive species, thus facilitating the generation of hydroxyl radicals (adapted from [61], images from pexels.com, free license). B) An overview of the composition of lignocellulosic biomass, the steps for application of the Fenton process and the final recovered products (adapted from [45,51]). The photo-Fenton process here could enhance Fe^{2+} cycling and hence achieve higher reaction kinetics.

i.e. lipids, instead of cellulose.

Nevertheless, this similarity led practice down the same treatment routes as terrestrial biomass [81]. The existing pre-treatment methods used are either physical-mechanical (e.g. disintegration, sonication [78,82–84]) or chemical methods [85], both of which are costly [86,87] and difficult to scale up [78]. Since chemical methods consume less energy (but still remained expensive), the pre-treatment with the Fenton process has been proposed as an effective alternative with up-scaling potential and low(er) reagent associated costs. The other major advantage comes from the application of Fenton in wet biomass, without the need for pre-drying, which would increase the costs [78,88–90]. In addition, the release of lipids in the liquid phase facilitates their extraction [91]. Finally, the use of the potent coagulant ferric iron forms also achieves simultaneous harvesting of the cells [90,92].

As far as the applications are concerned, the synergy of $FeCl_3$ for harvesting and lipid extraction has been successfully attained [92] and the use of H_2O_2, with or without Fe, has been effectively used to oxidize the *Chlorella vulgaris* cell [80]. Modelling the process developed a greater understanding of the cell disruption mechanism and fatty acid methylesters composition [80]. A doubled yield in lipid amounts was attained, and a higher quality of fatty acid methylesters was produced [78]. In parallel, exploiting the harvesting process alongside disruption sparked important research on high yields in extraction [90,93] as well as highlighting the apparent benefits of applying UVA light in this process to induce the photo-Fenton treatment, which resulted in a reduction of reagents costs [94]. Finally, instead of the valorization of algal lipids, a Fenton-based process (i.e. Fenton with heating) has been employed to disrupt various algal cell walls and recover the contained polysaccharides while converting them to sugars; complete (100%) yield has been achieved, free of inhibitors (furfural by-products) and digestibility of micro- and macro-algal biomass. Since the polysaccharides are −OH rich, the $HO^\cdot$-mediated attack is facilitated, thus destroying the cellulose structure of algae, a key step to biodegradability increase [81,95].

These applications demonstrate the potential of the (photo)Fenton process in pre-treatment of biomass. Its use has to be promoted since the process is fairly simple. Fenton reagents are considerably cheaper than the existing chemical processing methods, and by using solar irradiation as a light source, the cost-effectiveness of the system can be further enhanced alongside the enhancement of yields when recovering high value products.

4. The Fenton process and cancer: the poison and the remedy

4.1. Fenton-mediated induction of malignant tumors - the ailment

According to the US National Health Institute, cancer is the sum of relative diseases which all present abnormal, uncontrollable cell division and expansion to neighboring tissues [96]. Its severity positions

cancer as one of the deadliest conditions, leading to approximately 8.2 million cancer-related deaths around the world. Although this review will not deal with the exogenous factors that ultimately lead to carcinogenesis, some of the most widely known contributing factors are exposure to chemicals and irradiation (ionizing or UV) [97]. Nevertheless, there are less well known factors that the general public are not aware of, involving iron overloading [98]. Before discussing how iron participates in carcinogenesis, a brief presentation of the process will be provided.

The formation of cancerous cells lies within the reactive oxygen species' (ROS) balance inside the cell. Under normal conditions, ROS are present as a part of oxygen metabolism [99–101] and serve as an intracellular messenger, but their mis-regulation can lead to oxidative stress and in turn a cascade of issues [98,102,103]. The most common intracellular ROS are superoxide radical anion and H_2O_2, originating from mitochondria, microsomes and peroxisomes, P450 cytochrome, xanthine oxidase, NADPH oxidase and others [98]. Although $O_2^{\bullet-}$ is not highly oxidative and its reactivity is rather limited (compared to other ROS like $HO^{\cdot}$), its toxicity is induced via the implications brought about by further metal-catalyzed ROS production [23,98,104]), especially Fe (from hemoglobin and other enzymes [104,105]) and Cu. Their release initiates an intracellular Fenton (or Fenton-like, for Cu) reaction, resulting in the production of the highly oxidative $HO^{\cdot}$ [102]. Furthermore, its participation in the reaction is encountered as a reductive species for Fe^{3+}, which can enhance its regeneration to Fe^{2+} and reintroduction to the catalytic cycle. The presence of H_2O_2 fuels this process, which, despite producing a very short-lived ROS, can react with virtually any component close to its generation [99,106].

Through the aforementioned Fenton process, it is clear that under physiological conditions, the presence of iron is not carcinogenic, since it is necessary among others for O_2 transport and DNA synthesis [107–109]. As such, it is tightly regulated inside the cell [110,111]. Nevertheless, this version of the Fenton reaction is related with the normal ageing process [98,112], thus playing a dual role in cell cycle [109]. One main reason carcinogenic events would occur if for any reason an organism presents an iron overload [101,103,113,114], due to an illness (e.g. hemochromatosis) [98,104,115] or high iron consumption/accumulation (nutrition factor) [103], for instance. This readily available, chelatable iron that remains un-sequestered by Fe/S clusters or hemes [116–118] leads to a compartment known as “labile iron pool”, LIP [98,104,119]. In theory, it is only a small percentage of the total iron, since iron is mainly liganded to other proteins (e.g. heme [120]). However, the LIPs' implications are important [121]. As a result, DNA damage has been considered as the first target of iron-mediated (Fenton) intracellular damage and the initiation step of carcinogenesis [112,122], via erratic transcription, signaling or genome instability [123,124].

Another reason lies in oxidative stress itself. As initially stated, the reactive species are not necessarily harmful, but mediate necessary functions of the cell (e.g. signaling [125]), and even cause cell proliferation [126]; their character changes with higher concentrations, which leads to cell death [98,102]. However, different types of cell may require different levels of damage [102]. To reach this state, the nucleic and mitochondrial DNA damages [127], particularly to the ribose ring and nucleobases [102], initially cause mis-repairs in the dividing cells (with subsequent neoplastic state [128–130]) or the imbalance between cell growth and death. Consequently, the initiation process presented previously gives way to the promotion phase, which is closely dependent on the presence of iron [109,131–133], and end with the irreversible progression phase [98], due to long term oxidative stress by the Fenton process [101,103,113,134] in cytosol or mitochondria [118]. A brief description of the pathway to carcinogenesis is given in Fig. 3a.

However, not every aspect of the Fenton process is a disadvantage when it comes to cancer. Since there is an obvious metabolic imbalance in these cells [103,109,133], where a deficiency in antioxidants [142] leads to the high ROS concentration for signaling reasons [102] or the apparent dependence of tumor growth development to iron [103,118,133,143], incapability to expel Fe [103] etc., one can take advantage of these behaviors when treating malignant tumors. Over the past few years, some chemodynamic therapy approaches have been proposed, such as induced ferroptosis [144], that differ from older approaches such as iron chelation by drugs [145,146] since direct induction of the (photo)Fenton process has been proposed as more effective [103]. Next, the advances in cancer treatment are summarized and the strategies to combat tumors via the (photo)Fenton reaction are presented.

4.2. The (photo)Fenton process as a treatment strategy - the cure

In principle, killing tumor cells by the Fenton process relies on the same principles as increasing its production of hydroxyl radicals. As such, the following aspects should be considered: i) increasing the concentration of Fe, ii) augmenting H_2O_2 levels, iii) lowering the pH, iv) introducing UV–vis light and v) heat stimulation. Naturally, higher Fe concentrations will lead to higher $HO^{\cdot}$ production (if not limited by H_2O_2 concentration); acidic values will help maintain the Fe soluble (or else, chelation/fixing will be necessary); light will enhance the photo-regeneration of Fe^{3+} to Fe^{2+} and as an Arrhenius-controlled process, higher temperatures work in its favor. Alternatively, ROS suppression has been proposed as an approach, since they are of upmost importance to cancer cells [102,147–150]; interested readers should refer to the aforementioned references, as they are not actually Fenton enhancers and this strategy will not be reviewed here. Ultimately, other combinations/enhancements of the Fenton process will be assessed (drugs, ultrasound, other metals). A schematic overview is given in Fig. 3b.

4.2.1. Increasing Fe concentration in cancer cells

The majority of reviewed work falls within this category, thus highlighting its importance. When the production of Ferritin, a major iron-chelating protein, for instance, was blocked, it was found to induce higher ROS via larger quantities of free iron [151]. In addition, when Fe^{2+} was chelated by bipyridyl, the intracellular damage was increased [152], showing how critical it is to have Fe^{2+} available to react into the cells. However, since it is difficult to directly introduce Fe^{2+} to induce Fenton, particular attention has been given to creating materials that release it in the cell. There are a number of advantages to these smaller versions of iron particles (nano-sized ones [150,153,154]) suitable in cancer treatment, since they have a long shelf life, easy renal release from the body, high precision in the application (not targeting all cells), can be functionalized, covered or loaded with therapeutic agents [155–161] but still suffer from some disadvantages such as the low accumulation in tumor cells [162].

In the existing literature, the greatest merit belongs to Fe-related nano-particles [103,162] and its 1st application was an iron oxide nanoparticle [163]. This family of Fe materials suitable for cancer treatment include amorphous Fe0 nanoparticles [164] or nanocrystals [165,166], metal-organic frameworks (MOFs [137,167]), nano-oxides (IONPs, [168–170], interested readers should also refer to [162,150,166] and references therein) and bimetallic ones ($SnFe_2O_4$, $MnFe_2O_4$ or FePt ones [171–173]). MOFs and IONPs, in particular, have extremely large surface areas and exhibit excellent catalytic properties [174,175]. These materials preferably should be designed to release Fe in the lysosome, which is acidic and allows their participation in the Fenton process [162]. The nano-particles have also been found to be less toxic [176], most probably due to their introduction in a non-elemental form [103,162].

4.2.2. Increase of intracellular H_2O_2 levels

H_2O_2 in tumor cells is 5x higher when compared with their healthy counterparts [177,178]. This effect and the discovery of low catalase levels in tumor cells (hence higher H_2O_2 amounts) further promoted the idea to create materials that can materialize this into oxidative $HO^{\cdot}$

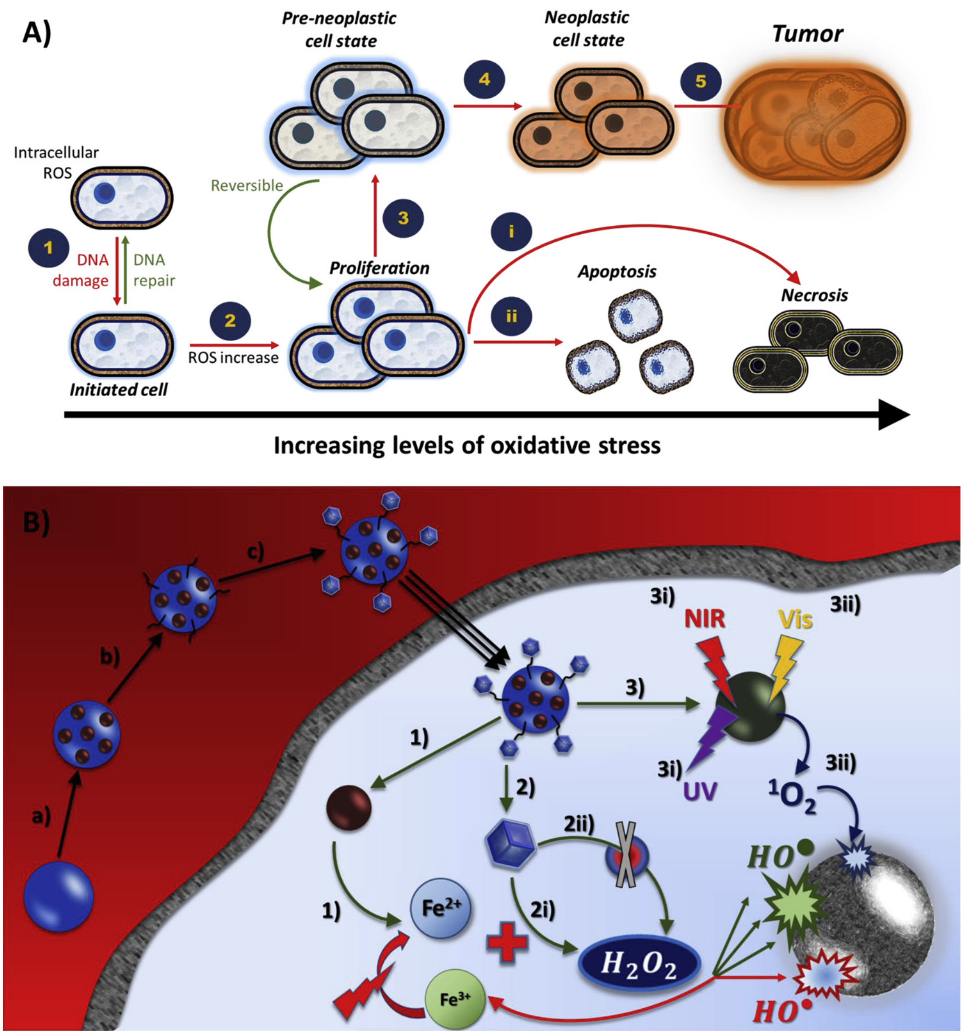

Fig. 3. Tumorigenesis and its treatment by the (photo)Fenton process. A) The cell is under normal ROS conditions, and the following actions need to occur to end up in tumors: 1) elevated ROS, 2) further elevation in levels that cannot be regulated, 3) the high ROS levels cause the cells to proliferate and normally an apoptotic or necrotic response is induced (i,ii), depending on the ROS levels; in the opposite case the cells enter a pre-neoplastic state, 4) the intracellular stress leads to neoplastic state, which is no longer reversible and 5) the cells are considered a tumor (adapted from [98,135]). B) The majority of applications against cancerous cells involve a material, a) a proper support for Fe (e.g. MOFs), b) are functionalized, c) bear an antitumor drug or substance that falls within one of the strategies to combat cancer (see text for details). The cell has a ROS generation by Fe^{2+} and H_2O_2, which generates $HO^{\cdot}$ (red line pathway). After the passage to the nano-agent into the cell, the following major categories happen: 1) release of Fe nano-particles, 2) liberation of agents that produce H_2O_2 (2i) or inhibit the controlling enzymes (2ii); all generate further $HO^{\cdot}$ (green line pathways), 3) add/bear compounds that convert NIR light to UV (3i) or combine photodynamic therapy agents such as singlet oxygen production (3ii), while light could be provided to regenerate Fe^{3+} back to Fe^{2+} and re-participate in the Fenton cycle (adapted from [136–141]) (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

damage. Nevertheless, these concentrations are not high enough to effectively act as a Fenton catalyst [166,179]. It stands to reason that H_2O_2 is the limiting factor, in the iron-rich tumor environment or the newly-introduced Fe in the cell. As such, following the discovery that pharmacological ascorbate [180] or cinnamaldehyde [181] increases H_2O_2 levels, their introduction (ascorbic acid and benzoyloxycinnamaldehyde, respectively) with a ferrocene-based material was performed [181,182]. Furthermore, a nano-magnetite-based mesoporous material with glucose oxidase, which reacts with cell glucose to generate H_2O_2, was assessed [136]; the last two strategies also contained iron which enhanced tumor suppression by $HO^{\cdot}$ generation. It is worth nothing that the glutathione would have to be low, since it is an antioxidant enzyme [166].

4.2.3. Lowering the pH of the tumor environment

In order to avoid precipitation of Fe in the near-neutral environment of tumor cells, reducing the pH of the tumor micro-environment (pH 6.5–7) is a favorable approach. Alternatively, the delivery of the iron nano-materials has to be attained in tumor endosomes (pH 5) or lysosomes (pH 4.5) [183]. It was discovered that induction of cell acidity, followed by Fe release and H_2O_2, can be achieved through an amorphous nano-iron oxide platform [183].

4.2.4. Heat-induced increase of Fenton reaction efficiency

The literature does not have many examples to offer on heat-induced Fenton-mediated killing of cells, since heating, more specifically hyperthermia, is another process of tumor destruction, which works synergistically with drugs or radiation. However, it is a field worth exploring and as such the use of pyrite nanoparticles was assessed in their capacity to promote photo-thermal reactions powered by a near-infrared laser, which in turn enhanced the Fenton reaction [184].

4.2.5. Shedding light to induce the photo-Fenton process

The use of light to combat cancer is an existing strategy and has been used effectively in other applications, such as photo-dynamic therapy (PDT). The tunable, modulated character of light (wavelength, intensity etc.) makes it an interesting Fenton enhancement for tumor cell destruction [166]. Light-triggered applications involve the effective generation of $HO^{\cdot}$, alongside $^1O_2$ generation, thus enhancing the photochemical aspects of tumor killing [140]. Nevertheless, UV light penetration is inversely correlated with its penetration length, meaning its direct application is hindered. As such, the literature uses the example of a graphene oxide/iron oxide nano-agent in which near-infrared light is absorbed by the material, which promotes electrons and their reaction with O_2 to generate $O_2^{\bullet -}$; in turn this disproportionates to H_2O_2 and reacts with Fe to generate $HO^{\cdot}$ [138]. Another instance is the use of manganese-ferrite or magnetite nanoparticles that are modified to bear photo-sensitizers, but predominately for PDT enhancement by the Fenton process these nanoparticles mediate [141,185]. In addition, since the use of UV is problematic, the application of up-conversion lanthanide materials can yield interesting results; a photo-Fenton application with near-infrared light initiation has been already effectively applied for apoptosis induction [139].

4.2.6. Ultrasound-mediated enhancement of tumorigenic activity

The scientific rationale behind sono-assisted intervention lies in the ability of cavitational bubbles to generate high temperatures and pressure anomalies, which, in turn, gives rise to superoxide and hydroxyl radicals [186,187]. Since one of the main approaches to tumor elimination is the enhancement of ROS, the sonoluminescence process that takes place during cavitation bubble implosion is critical in order to achieve higher intracellular ROS contents. Furthermore, the cavitational collapse of capsules induced during ultrasound imaging was exploited, filling the capsules with an H_2O_2-based material encapsulated in a polymer that bears magnetite nanoparticles. As such, directed detection and selective application was attained [188].

4.2.7. Drug-based chemotherapy combined with ROS induction, and alternative metal sources

It has been reported recently that β-lapachone, an anticancer drug, induced the production of high H_2O_2 amounts in the cell, and its delivery by pH-sensitive IONPs enhanced the effectiveness of treatment [189]. In addition, doxorubin, which enhances H_2O_2 production, combined with FePt-magnetite nano-particles, effectively killed cancer cells without the loss of normal ones [190]. In another approach, doxorubin was used in conjunction with 3-amino-1,2,4-triazole, combining the known action of doxorubin and 3-amino-1,2,4-triazole inhibits catalase. This caused further $HO^•$-mediated damage since more H_2O_2 was available for the Fenton process. Copper is known to drive a Fenton-like process, with the concomitant production of $HO^•$. As such, by coupling copper-based nano-materials with drugs, effective tumor cell killing was attained. A first example was mesoporous Cu-Si nanoparticles loaded with 3-amino-1,2,4-triazole for catalase inhibition, hence a metal and higher amount of H_2O_2 led to higher ROS production [191], whereas the combination of doxorubin with a nano-hybrid system further disturbed mitochondrial membrane integrity [192].

To conclude, the possibilities of modulating the (photo)Fenton process for cancer treatment are truly endless. Nevertheless, special attention should be given to the topics of biocompatibility and toxicity of the selected catalysts and in parallel, higher specificity against tumor cells compared to healthy ones. It has been a long expressed concern that iron overload therapies will attract a certain level of skepticism [103], but the simultaneous development of advanced nanomaterials and toxicity assays to control their application, the battle against effective tumor suppression can still be won.

5. General bio-medical applications of the (photo)Fenton process

5.1. Design of new antibiotics and antimicrobial strategies based on the Fenton process

One of the key functions of designing new, potent and highly selective antibiotics is to take advantage of the components of the bactericidal mechanism of the drugs. With antibiotic resistance on the rise, the problem is timelier than ever, and necessitates going beyond the more typical approaches in drug design [193–195]. More specifically, the bactericidal drugs produce ROS in order to inactivate the microorganisms [195,196]. The pathway to inactivation usually involves the reaction of Fe from intracellular components with H_2O_2 (from $O_2^{\bullet-}$) in order to maintain a catalytic cycle of $HO^•$ production and exert a bactericidal action [195]. While the generation of the hydroxyl radical is most desirable, an in-depth understanding of the participation of lesser ROS in the process, such as the superoxide radical, can lead to the creation of equally potent drugs. Superoxide is very selective (preferentially damaged bacterial and not mammalian cells [196]), and is key to attacking the iron/sulfur clusters that hold the key to the Fenton process [195]. The recent discoveries surrounding the role of Dps, a ferritin-like protein, and its protective capacity during oxidative stress, indicate that blocking this pathway allows the Fenton process to act [197], hence new drugs could indirectly induce the Fenton process. Finally, exploiting the Fenton process could alleviate the post-burn infections in affected patients. It has been proposed that the treatment of wounds with the Fenton reagents can be an ally against opportunistic bacterial pathogens [198], especially the resistant type prevailing in hospital environments. It is more than likely that, the presence of blood, plasma etc. would require special care and optimization of the application, but the goal would be to inactivate bacteria before the human cells and/or rely on the regeneration of the latter.

5.2. The (photo)Fenton process and dental hygiene

The (photo)Fenton process and its antimicrobial activity has recently started to be exploited in endodontic disinfection, especially root canals. The existing strategies involve the use of chemicals, such as hypochlorite or chlorhexidine [199,200]. The majority of the disinfection studies on (photo)Fenton use *E. coli* or *enterococci* as a bacterial model, but in fact, their abundant presence in filled teeth has been confirmed [201,202]. This microorganism, along with others, have been shown to create biofilms [203,204], and previous experience in water treatment has demonstrated that typical chemical disinfectants, such as chlorine [205], fail to penetrate the films sufficiently and clean the deposited bacteria. As a result, the inactivation of a series of bacteria has been attained by $HO^•$-mediated inactivation by 405 nm laser photolysis of H_2O_2 [206,207], which naturally allows a photo-Fenton process to do a similar function. An overall scheme is given in Fig. 4a.

This process has been studied with H_2O_2 and ferrous gluconate as Fenton reactants, in the presence of light [199]. Even with low irradiance values (non-germicidal), higher inactivation capacity than photolytic $HO^•$ production was attained and found to be comparable to hypochlorite. Finally, the use of (-)-epigallocatechin-3-gallate (EGCG), demonstrated antibacterial effects [208], typical of polyphenolic substances [209,210]. In this respect, it is worth exploring a photo-assisted Fenton process with polyphenols, a safe and suitable method for effective root canal disinfection.

Besides disinfection, the use of H_2O_2 in bleaching and teeth whitening has been in application for several years. A description of the process is given in Fig. 4b. Studies have shown that the radical-based processes of H_2O_2 photo-lysis enhance the removal of stains by antibiotics [211]. It is thus possible that a photo-Fenton process would be superior. Given that H_2O_2 penetrates the enamel [212], low energy wavelengths (visible light) have higher penetration capacity. In addition, the utilization of a broad-spectrum light source will increase the iron action, contributing to the ferric to ferrous cycling, hence the photo-Fenton reaction is rising as a potent whitening process [200], with rhodamine dye and tea stains have been both removed [200,212].

6. Conclusions and perspectives

The (photo)Fenton process, as discussed in this review, is one of the most straightforward (sets of) reactions, yet its presence is implied in some of the most complex phenomena in biology and chemistry. It was shown that the ubiquitous character of iron and the availability of H_2O_2, either in-situ generated or added, as a cheaper oxidant alternative, has promising applications in a series of environmental and other domains. Most often, in the applications presented, the Fenton reaction is an easy, simple, cheap or environmentally benign process to pre-treat a material and modify its initial properties (surfaces, biomass). The second significant category relies on the generation of the highly oxidative hydroxyl radicals to oxidize biological matter, such as biomass or cancer cells, or inorganic one (teeth enamel). In some cases, an inexpensive process has led to the generation of high-value products (nano-particles, biomass), which further motivates research into the corresponding topics. In each application, the principles were preserved and the focus has been centered on how to modulate the basic rules (pH, concentration of reagents, light) into the needs of each niche.

It is evident that in order to widen the range of applications and the

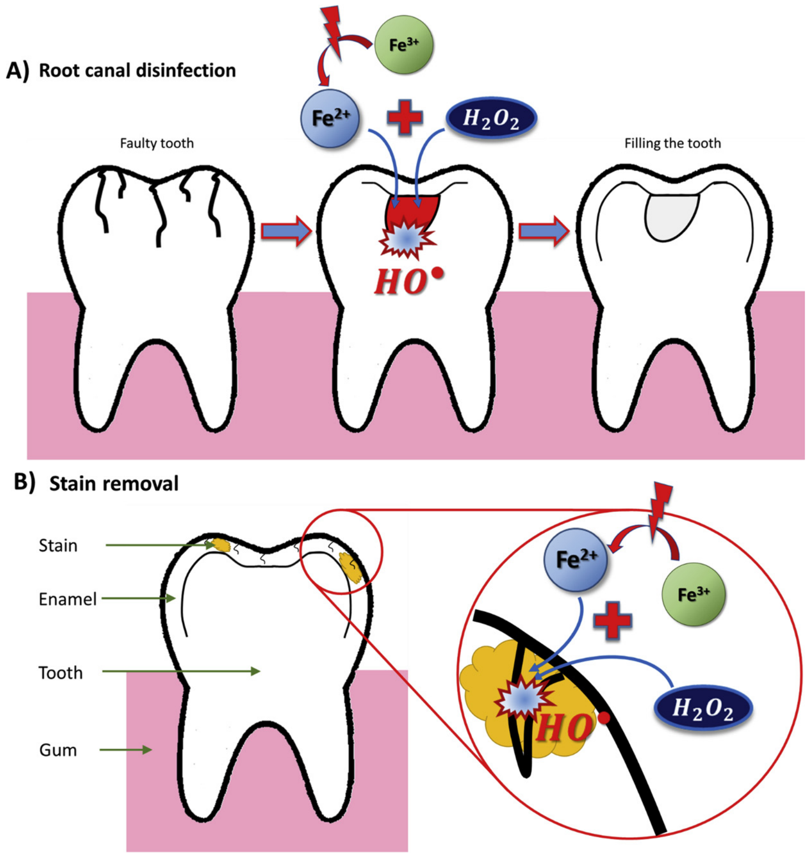

Fig. 4. Application of the (photo)Fenton process in dentistry. A) The Fenton process is proposed to be used for root canal disinfection, instead of traditional chemical disinfectants. B) Removal of stains (or teeth whitening) can be attained by the photo-Fenton process, since Fe^{2+} and H_2O_2 can penetrate the enamel and allow the generation of $HO^{\cdot}$ closer to the stain target. In each case proper light sources might induce the catalytic, photo-Fenton cycle.

acceptability of the process, there are certain parameters that still need to be resolved. For example, i) there are often limitations in the existing fields of application that hinder its application (e.g. potent sensors for human cells), ii) the associated reagent costs have to be lowered or replaced with cheaper alternatives, iii) in industrial applications, focus must be given in the concurrent environmental legislation, iv) novel reactor designs for its application must be developed, v) the toxicity of Fe nanoparticles has to be scrutinized, vi) most of the processes are small, bench scale, of limited capacity and vii) find a framework for ethical clearance in human testing for cancer research. These are only some of the aspects that remain under development, as more real-life, large-scale applications are necessary to truly advance the field. The Fenton research community must further elaborate the recent applications presented in this review (as no topic is older than 5 years), couple the efforts with material science or chemical engineering, biomedicine, dentistry, and attract industrial partners to work towards the intensification of the process. The possibilities are truly endless.

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